#13/ K.T. Appeal Brief

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**RTS-0348**
Inventors:	**Bennett and Freier**
Serial No.:	**10/003,354**
Filing Date:	**December 6, 2001**
Examiner:	**Terra C. Gibbs**
Group Art Unit:	**1635**
Title:	**Antisense Modulation of Phosphatidylinositol-4-Phosphate 5-Kinase Iα Expression**

"Express Mail" Label No. **EL977826931US**
Date of Deposit **September 16, 2003**

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APPEAL BRIEF

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Appendix 1 - Pending Claims

I. Real Party of Interest

The real party of interest is Isis Pharmaceuticals, Inc., assignee of all rights, title and interest in the instant application.

II. Related Appeals and Interferences

Appellants are not aware of any related appeals or interferences.

III. Status of Claims

Claims 3, 11 and 16-20 are canceled.

Claims 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 and 15 are pending.

Claims 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 and 15 are rejected.

A copy of pending claims 1, 2, 4 through 10 and 12 through 15 is attached hereto as Appendix 1.

IV. Status of Amendments

All amendments to the claims have been entered upon this appeal.

V. Summary of the Invention

The claimed invention relates to compounds and methods for modulation of phosphatidylinositol-4-phosphate 5-kinase, Iα expression. The compounds of the instant invention are antisense oligonucleotides from 8 to 50 nucleobases in length targeted to specific nucleobase regions within the sequence of phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3. The compounds also may contain certain modifications to enhance their stability and activity, including the addition of modified internucleoside linkages, such as phosphorothioate linkages, modified sugar moieties, such as 2'-O-methoxyethyl sugar moieties, and modified nucleobases, such as 5-methylcytosine. The compounds of the instant invention also include chimeric oligonucleotides, and compositions wherein the compounds are administered in pharmaceutically acceptable carriers or diluents, including colloidal dispersion systems. The present invention is also a method of inhibiting the expression of phosphatidylinositol-4-phosphate 5-kinase, Iα *in vitro* that comprises contacting cells or tissues with the compounds of the present invention.

VI. Issues

The issue on appeal is whether claims 1, 2, 4-10 and 12-15 are unpatentable under 35 U.S.C. § 103(a) as being obvious over

Honda et al. (1999) and Loijens et al. (1996), and further in view of Weintraub (1990), Baracchini et al. (US Patent 5,801,154), and Fritz et al. (1997).

VII. Grouping of Claims

Claims 1, 2, 4-10 and 12-15 stand or fall together on the issue of obviousness under 35 U.S.C. § 103(a).

VIII. Arguments

A. Rejection of Claims Under 35 U.S.C. 103(a)

The Examiner has rejected claims 1, 2, 4-10 and 12-15 under 35 U.S.C. § 103(a) as being unpatentable over Honda et al. (1999) and Loijens et al. (1996), and further in view of Weintraub (1990), Baracchini et al. (US Patent 5,801,154), and Fritz et al. (1997). The Examiner suggests that one of ordinary skill in the art would have been motivated to make antisense nucleic acids targeting phosphatidylinositol-4-phosphate 5-kinase, Iα since Honda et al. (1999) and Loijens et al. (1996) teach phosphatidylinositol-4-phosphate 5-kinase, Iα involvement in membrane ruffle formation, regulated secretion and signal transduction. The Examiner suggests it would have been obvious to make antisense compounds encoding phosphatidylinositol-4-phosphate 5-kinase, Iα since Weintraub (1990) taught antisense nucleic acids can selectively inhibit the activity of genes and

gene expression and antisense techniques are tools for probing the function of individual genes. The Examiner suggests that one of ordinary skill would have had a reasonable expectation of success in modifying antisense oligonucleotides since the prior art has taught the desirable benefits of such oligonucleotides as described by Baracchini et al. (US Patent 5,801,154) and Fritz et al. (1997).

Appellants respectfully disagree with the Examiner's suggestions regarding the rejection under 35 U.S.C. 103(a).

1. Summary of the Teachings of Each Reference Cited Under 35 U.S.C. 103(a)

Honda et al. (1999) disclose only the biological role of phosphatidylinositol-4-phosphate 5-kinase, Iα as a downstream effector of small G protein ARF6 in membrane ruffle formation. Nowhere does this reference teach or suggest use of antisense compounds of any type to target the phosphatidylinositol-4-phosphate 5-kinase, Iα gene and to inhibit its expression using antisense. As a result of failing to teach or suggest use of antisense compounds, this reference also fails to teach or suggest antisense compounds as now claimed.

Loijens et al. (1996) disclose the peptide sequence of phosphatidylinositol-4-phosphate 5-kinase, Iα isolated from

bovine erythrocytes and then the full-length cDNA coding phosphatidylinositol-4-phosphate 5-kinase, Iα and two predicted splice variants that were cloned from a human fetal brain cDNA library. The paper reports the distribution of phosphatidylinositol-4-phosphate 5-kinase, Iα in tissues. However, nowhere does this paper teach or suggest antisense compounds of any type targeted to any nucleobase region within a target region of phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3 as claimed. It is only with the specification in hand that one of skill has evidence that targeting antisense to regions of phosphatidylinositol-4-phosphate 5-kinase, Iα could successfully inhibit expression of this gene.

Therefore, neither of the primary references, either alone or when combined, teach or even suggest use of antisense compounds of any type for inhibition of expression of phosphatidylinositol-4-phosphate 5-kinase, Iα, including antisense compounds as claimed. The secondary references cited fail to overcome the deficiencies in teaching of these primary references.

Weintraub (1990) is an older paper on the technology of antisense and only discusses the use of antisense as a research tool. Nowhere does this paper teach or suggest antisense compounds of any type targeted to

phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3 as claimed. Additionally, this paper explicitly states at page 46 that "many important refinements of antisense technology are still needed, and many important questions must still be answered..." Thus, one of skill in the art would not understand using this paper that antisense technology would be successfully used to inhibit expression of any gene, without evidence of such use.

Baracchini et al. (US Patent 5,801,154) disclose antisense oligonucleotides and their use to inhibit expression of multi-drug resistance-associated protein. The patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target a specific gene, phosphatidylinositol-4-phosphate 5-kinase, Iα, or specific nucleobase regions of this gene, and the successful inhibition of expression using antisense. The teaching of antisense, in general terms, to the coding region of a different gene does not provide one of skill with the evidence that antisense compounds targeted to specific nucleobases regions within a coding region a different gene would be successful at inhibiting expression of that gene.

Fritz et al. (1997) is a paper that describes carrier systems for antisense oligonucleotides, in general terms, and specifically discloses cationic polystyrene nanoparticles. Nowhere does this paper teach or suggest antisense compounds of any type targeted to any nucleobase region within the phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3 as claimed.

Therefore, Appellants respectfully disagree with the Examiner's suggestion that this combination of prior art references establishes a *prima case* of obviousness.

2. Three Basic Criteria of *prima facie* Obviousness

In accordance with MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations. The prior art combinations cited under 35 U.S.C. 103 by the Examiner fail to teach or suggest all of the limitations of the claims, and fail to provide either the motivation to modify the reference or the expectation of success.

3. The Cited Art Fails to Teach the Limitations of the Claims

Any combination of the cited prior art fails to teach or suggest the limitations in the claims, namely compounds from 8 to 50 nucleobases in length targeted to specific nucleobase regions (*i.e.*, nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region) within the sequence of phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3. None of the references cited by the Examiner teach or suggest antisense compounds targeted to this gene, phosphatidylinositol-4-phosphate 5-kinase, Iα. Since none of these references teaches or suggests, either alone or when combined, antisense to phosphatidylinositol-4-phosphate 5-kinase, Iα then they cannot teach or suggest antisense targeted to specific nucleobase regions within the sequence of this gene. Both the MPEP and case law are quite clear. To establish *prima facie* obviousness of a claimed invention, all the limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) and MPEP 2143.03. Since none of the prior art references, either alone or when combined, teach or suggest the

limitations of antisense that targets specific nucleobase regions within phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3, the cited combination of art cannot render the instant invention obvious as set forth in claim 1 or dependent claims 2, 4-10 and 12-15.

4. The Combined References Fail to Provide Motivation

The cited combinations of references also fail to establish a *prima facie* case of obviousness because the motivation to combine these references is lacking. The teaching or suggestion must be found in the prior art and not based on applicant's disclosure. *In re Vacek*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that the cited references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. MPEP 2143.01. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). It is only with the specification in hand that one of skill would have been motivated to make antisense compounds to the specific nucleobase regions within the sequence of phosphatidylinositol-4-phosphate 5-kinase, Iα as claimed.

Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143),

any of the combinations of the cited references fail to make claim 1, and by dependency claims 2, 4-10 and 12-15 obvious.

5. The Cited References Fail to Provide a Reasonable Expectation of Success

None of the references cited by the Examiner under 35 U.S.C. 103(a) would not provide one of skill with any reasonable expectation of success for using antisense compounds as claimed to inhibit expression of phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3. It is only with the specification in hand that one of skill would understand that antisense compounds targeted to the claimed nucleobase regions within the sequence of phosphatidylinositol-4-phosphate 5-kinase, Iα of SEQ ID NO: 3 would have activity to inhibit expression of this gene. None of the references cited by the Examiner would point one of skill to the claimed nucleobase regions as being ones to target in particular. MPEP 2143 states that some degree of predictability is required in order to establish an expectation of success. However, the paper cited by the Examiner by Weintraub (1990) points out that important refinements to antisense technology are still needed. Further, data provided in the patent by Baracchini et al. (US Patent 5,801,154) show that only certain antisense

compounds targeted to multi-drug resistance-associated protein had activity to inhibit gene expression. Therefore, these papers, the only two cited by the Examiner to teach antisense compounds of any type targeted to a gene, actually teach that antisense technology is not always predictable. Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143), these combined references fail to make claims 1, 2, 4-10 and 12-15 obvious.

IX. Conclusion

The references cited by the Examiner clearly do not provide the requisite teaching or suggestion to render the claimed invention obvious. Withdrawal of the rejection under 35 U.S.C. § 103(a) is, therefore, respectfully requested.

Respectfully submitted,

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Appendix 1 - Pending Claims

Claim 1: A compound 8 to 50 nucleobases in length targeted to nucleobases 83 through 355 of a 5'-untranslated region, nucleobases 458 through 2045 of a coding region, nucleobases 2050 through 2069 of a stop codon region, or nucleobases 2063 through 3659 of a 3'-untranslated region of a nucleic acid molecule encoding phosphatidylinositol-4-phosphate 5-kinase, Iα (SEQ ID NO: 3), wherein said compound specifically hybridizes with one of said regions and inhibits the expression of phosphatidylinositol-4-phosphate 5-kinase, Iα.

Claim 2: The compound of claim 1 which is an antisense oligonucleotide.

Claim 4: The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

Claim 5: The compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage.

Claim 6: The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified sugar moiety.

Claim 7: The compound of claim 6 wherein the modified sugar moiety is a 2'-o-methoxyethyl sugar moiety.

Claim 8: The compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified nucleobase.

Claim 9: The compound of claim 8 wherein the modified nucleobase is a 5-methylcytosine.

Claim 10: The compound of claim 2 wherein the antisense oligonucleotide is a chimeric oligonucleotide.

Claim 12: A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

Claim 13: The composition of claim 12 further comprising a colloidal dispersion system.

Claim 14: The composition of claim 12 wherein the compound is an antisense oligonucleotide.

Claim 15: A method of inhibiting the expression of phosphatidylinositol-4-phosphate 5-kinase, Iα in cells or tissues comprising contacting said cells or tissues in vitro with the compound of claim 1 so that expression of phosphatidylinositol-4-phosphate 5-kinase, Iα is inhibited.